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PD

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/981,310	12/16/97	LANDEGREN U	1209-121P

002292 HM12/1119
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EXAMINER	
PORTNER, V	
ART UNIT	**PAPER NUMBER**
1641	16

DATE MAILED: 11/19/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 08/981,310	Applicant(s) Landegren
	Examiner Portner	Group Art Unit 1641

☒ Responsive to communication(s) filed on *Sep 8, 1999* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-6 and 8-10* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-6 and 8-10* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Claims 1-6 and 8-10 are pending.

Rejections Maintained

1. Claims 1, 3-5 remain rejected under 35 U.S.C. 102(e) as being anticipated by or in the alternative as being obvious over Birkenmeyer et al (US Pat. 5,667,974) for reasons of record.

2. Claims 1, 3-5 remain rejected under 35 U.S.C. 103(a) as being obvious over Nickerson et al (1992) or Delahunty et al (1995) or Kwok et al (1992) or Nilsson et al (1994)for reasons of record

3. Claims 1-6 and 8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (US Pat. 5,026,653) in view of Dattagupta and Ciechanover et al (US Pat. 5,384,255) for reasons of record as applied to claims 3-5 and 8.

4. Claims 1-4 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hendrickson et al (reference submitted on Applicant's IDS) for reasons of record.

5. Claims 6, 8-10 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling as essential reagents for conducting the method are not included in the claim and therefore remain rejected for reasons of record.

6. Claims 8-10 remain rejected under 35 USC 112, second paragraph for reasons of record as the claims do not distinctly claim Applicant's invention.

Response to Arguments

7. Please Note: Response to arguments made over reference removed will not be addressed.

8. **Birkenmeyer** et al is argued to not tech that "[t]he signal as being generated from the conjugation and amplification of the oligonucleotides on the second and third affinity reagents which the second and third affinity reagents are closely bound to the same antigen

7. Applicant's arguments filed with respect to Birkenmeyer et al have been fully considered but they are not persuasive because the reference teaches the detection of the amplified products which are immobilized on a solid phase carry a directly detectable label and the immobilized amplified products can be detected directly. Therefore, the amplified products are determined after the amplification and as a result of the amplification product. The incorporation of detectable components is only the result of the amplification process, therefore the reference teaches the newly amended claim limitation (see col. 8, lines 15-21; lines 49-52).

8. **Nickerson et al, Delahunty , Nilsson and Kwok** are argued to not disclose the use of antibodies in the method of detecting a macromolecule.

Applicant's arguments filed with respect to Nickerson et al (1992) or Delahunty et al (1995) or Kwok et al (1992) or Nilsson et al (1994) have been fully considered but they are not persuasive because the kits may be used for any purpose and in any method, and the affinity reagent is not limited to the determination of specific antigens but may be any affinity reagent to include lectins, receptors, single chain antibodies, cofactors or nucleic acids. Therefore the claims kits are not limited to antibodies for the determination of antigens. The cited references also meet the newly amended claim limitation:

a. Kwok and Nickerson both teach that upon amplification, the incorporation of digoxigenin labeled reporter oligonucleotide probe which is ligated to two other probes and only is incorporated upon the two biotinylated probes are aligned corrected and are not mismatched at

their target junction, wherein only after amplification can the analyte be detected (page 378, col. 2, third paragraph (oligonucleotide ligation assay).

b.Delahunty discloses the use of method using products which provide for the determination of an analyte only after the amplification of the affinity reagents and therefore obviates the newly amended claim limitations (see abstract, Figure 2, Discussion section and materials and methods).

c. Nilsson et al disclose the use of a padlock probe and two addition affinity reagents, wherein only those affinity reagents which were amplified through a ligase reaction retained there label after treatment with alkaline phosphatase (Figure 1, page 2086, col. 2, top of page; page 2067, col. 1, second full paragraph). Therefore, only those affinity reagents which were amplified were detectable when the affinity reagents were sufficiently close to each other that ligation could occur.

9. **Lee in view of Dattagupta** is argued to disclose assay methods which utilize two antibodies in a standard sandwich immunoassay format and Dattagupta et al "merely teach the conjugation of oligonucleotide to a protein" and do not suggest improving assay sensitivity by requiring the simultaneous binding of at least two probes to create a signal.

10. Applicant's arguments filed with respect to Lee in view of Dattagupta have been fully considered but they are not persuasive because Applicant focused on only one embodiment disclosed by Lee and Lee et al does disclose a three site or more immunoassay based on antigens

having three or multiple separate and distinct epitope binding sites, wherein two antibodies are in the soluble phase and are detectably labeled and at least one antibody is immobilized on the solid phase (Lee, col. 5, lines 1-68). Lee teaches that the use of multiple affinity reagents can: "increase the sensitivity of antigen binding assays", "eliminate the cross reactivity of antigen analogs", "eliminate the interference of circulating antibodies in human serum sample" and "eliminate interference from analogs of the antigen" (Lee, col. 6, lines 53-64). Therefore, contrary to Applicant's assertion that Lee do not suggest that this type of immunoassay format provides for increase assay sensitivity, Lee clearly teaches four advantages, to include increased assay sensitivity, for the use of multiple antibodies for the specific binding of multiple separate and distinct epitopes for the detecting the presence of a specific antigen. With respect to the assertion that Dattagupta et al "merely teach the conjugation of oligonucleotide to a protein", it is the position of the examiner that Dattagupta teaches far more than mere conjugation of a nucleic acid to a protein. Dattagupta teaches the amplification of nucleic acid-Protein A complex with IgG (col. 4, lines 58-62) and the use of the amplified reagent is therefore detectable in an immunoassay formats. The labeled reagent of Dattagupta is taught to provide an improvement over the prior art wherein the immunoassay is highly sensitive (col. 2, lines 51-58), and convenient. Dattagupta teaches that the use of a covalently linked IgG to a nucleic acid label provides for increased sensitivity and amplification of for the antigen antibody complex for detection is taught through the addition of a secondary reagent which increases, amplifies the detectable label (col. 4, lines 47-61).

11. Lee in view of Dattagupta and **Ciechanover** et al is argued to "fail to disclose the simultaneous binding of two or more probes to generate a signal, wherein the "respective oligonucleotides on the antibodies to become conjugated."

12. Applicant's arguments filed with respect to Lee, Dattagupta and Ciechanover have been fully considered but they are not persuasive because (see discussion of Lee in view of Dattagupta above) Ciechanover clearly teaches the use of ligase chain reaction for the amplification of two or more oligonucleotide which are ligated in the presence of a nucleic acid target which is then amplified (col. 19, lines 46-68). This section of the disclosure of Ciechanover is drawn to antibodies detectably labeled with a DNA and further discloses different art recognized means for the amplification of a oligonucleotide for increased ease of determining the presence of a single copy of DNA. The reference clearly defines means and methods for increasing immunoassay sensitivity. Therefore, claims 1-6 and 8 remain rejected for reasons of record on paper number 7.

13. **Hendrickson** is argued "There is not suggestion in Henderickson et al of the present kit which requires the conjugation of oligonucleotides on separately but closely bound affinity reagents to generate a signal."

14. Applicant's arguments filed Hendrickson et al have been fully considered but they are not persuasive because the recitation of intended use of a product is not further limiting of the claimed product. No specific sequences are recited in the claims, no ligase is included in the kit of claims 1-2. Therefore the first, second and third affinity reagents of Hendrickson et al obviate the

now claimed invention for reasons of record because the affinity reagents are only detected through the amplification of the conjugatable oligonucleotide label on the affinity reagent.

Amendment of the Claims/New Grounds of Rejection

Claims 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 9 recite the phrase ""crosslinkable oligonucleotides"; which lacks antecedent basis in the claim from which they depend.

Conclusion

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be changing February 7, 1998. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1641.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

November 18, 1999

James C. Housel

JAMES C. HOUSEL 11/19/99

SUPERVISORY PATENT EXAMINER